Liquid ventilation in the preterm neonate

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Introductory article

Partial liquid ventilaton with perflubron in premature infants with severe respiratory distress syndrome

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Background. *The intratracheal administration of a perfluorocarbon liquid during continuous positive-pressure ventilation (partial liquid ventilation) improves lung function in animals with surfactant deficiency. Whether partial liquid ventilation is effective in the treatment of infants with severe respiratory distress syndrome is not known.* **Methods.** *We studied the efficacy of partial liquid ventilation with perflubron in 13 premature infants with severe respiratory distress syndrome in whom conventional treatment, including surfactant therapy, had failed. Partial liquid ventilation was initiated by instilling perflubron during conventional mechanical ventilation to a volume approximating the functional residual capacity. Infants were considered to have completed the study if they received partial liquid ventilation for at least 24 hours.* **Results.** *Ten infants received partial liquid ventilation for 24 to 76 hours. In the other three infants, partial liquid ventilation was discontinued within four hours in favor of high-frequency ventilation, which was not permitted by the protocol, and the data from these infants were excluded from the analysis. Within one hour after the instillation of perflubron, the arterial oxygen tension increased by 138 percent and the dynamic compliance increased by 61 percent; the mean ($\pm$ SD) oxygenation index was reduced from 49 ± 60 to 17 ± 16. Chest radiographs showed symmetric filling, with patchy clearing during the return from partial liquid to gas ventilation. There were no adverse events clearly attributable to partial liquid ventilation. Infants were weaned from partial liquid to gas ventilation without complications. Eight infants survived to 36 weeks' corrected gestational age.* **Conclusions.** *Partial liquid ventilation leads to clinical improvement and survival in some infants with severe respiratory distress syndrome who are not predicted to survive.* (N Engl J Med 1996;**335**:761–7)

Surfactant replacement therapy, improvements in ventilatory strategies, and the widespread use of antenatal steroids have had an enormous impact on neonatal respiratory disease. The majority of babies with respiratory failure are now expected to respond to conventional time cycled, pressure limited ventilation with surfactant replacement therapy, and to survive.

However, as survival is not always assured, several alternative treatment modalities aimed at treating respiratory failure in sick babies, either as a primary treatment or rescue therapy, have been developed over recent years. The introductory article by Leach and colleagues describes the newest of these treatments – partial liquid ventilation (PLV) with perfluorocarbons. It is worthwhile briefly considering the current status of some of the other treatments in order to identify the possible role for PLV in the newborn and to understand the importance of critical evaluation of new technologies in neonatal intensive care.

Extracorporeal membrane oxygenation (ECMO)
ECMO employs a membrane oxygenator to effect gas exchange in an extracorporeal circulation and has been used successfully as an adjunct to ventilatory support in infants with reversible respiratory failure. The initial enthusiasm for ECMO led to its widespread use, particularly in North America, without any convincing evidence from large randomised controlled trials of its benefit over conventional treatments. However, a large multicentre randomised controlled trial of the use of ECMO for severe respiratory failure in term and near term neonates has recently been performed in the UK[1] in which the mortality in the group treated with conventional therapy was approximately 60% and ECMO halved the chance of death (RR with ECMO = 0.55 (95% CI 0.39 to 0.77)). The success of ECMO in this study was different with different diagnoses. A much better improvement in survival was seen in babies with meconium aspiration

syndrome than in those with congenital diaphragmatic hernia.

ECMO can only be applied to larger infants because of technical considerations, not least the difficulty in establishing adequate vascular access in smaller babies. It is not used routinely in preterm infants below 34 weeks gestation because of concern that the associated haemodynamic disturbance and the need for anti-coagulation may increase the risk of major intracranial haemorrhage.

The success of ECMO in managing severe respiratory failure in term and near term babies has thus been very impressive and any new treatments for such babies would need to be evaluated by comparison with ECMO. However, ECMO is not available for the treatment of small preterm babies with severe respiratory failure and other treatment modalities need to be evaluated.

High frequency oscillatory ventilation (HFOV)

This mode of ventilation relies on maximal recruitment of respiratory units to improve oxygenation by the use of a high mean airway pressure. The generation of rapid small tidal volumes using oscillation with active inspiration and active expiration improves elimination of CO_2. It has been suggested that the small changes in lung volume which occur during HFOV may decrease the risk of air leaks and bronchopulmonary dysplasia (BPD). This treatment is widely used as a rescue therapy in babies who do not respond to conventional ventilation. It has also been adopted by some neonatologists as the primary mode of respiratory support for babies with respiratory failure.

Several randomised controlled trials in neonates have shown short term improvements in gas exchange with HFOV compared with conventional mechanical ventilation.[2–4] However, the long term benefits from this mode of ventilation have unfortunately been less impressive to date.

There are no published randomised controlled trials of the use of HFOV as a rescue therapy in preterm neonates. The only published trial in term and near term infants found that the proportion of babies who responded to HFOV was not significantly different from those treated with continued conventional ventilation.[5] This study also failed to demonstrate a significant difference in mortality or the need for ECMO.

There are five published randomised controlled trials, involving some 822 subjects, comparing the use of HFOV against conventional ventilation as a primary means of respiratory support in preterm babies.[2–4 6 7] None of these trials has found an improvement in survival with HFOV use.

The effect of HFOV on development of BPD or air leaks is less clear. Two studies found no difference in the rate of BPD,[3 6] and a third did not report the incidence of BPD but found no difference in the need for ventilatory support at 30 days.[2] A further study[7] demonstrated a decrease in the incidence of BPD (defined as oxygen dependency and an abnormal chest radiograph at 36 weeks post-conceptional age) with HFOV, but no reduction in the need for supplemental oxygen at hospital discharge or in age at hospital discharge. The fifth study by Gerstmann *et al*[4] also found less BPD (defined as a lower "chronic lung disease score" at 30 days) in those babies treated with HFOV, and fewer of the babies receiving HFOV required supplemental oxygen at hospital discharge, although the mode of ventilation used did not predict independently

the need for home oxygen therapy in a multiple logistic regression analysis.

Only one of the five studies found a reduction in the incidence of air leaks in babies receiving HFOV[2] and this was mostly due to a reduction in mild pulmonary interstitial emphysema. There were significant concerns raised by two studies in which an increased incidence of intracranial haemorrhage occurred in babies receiving HFOV,[2 6] although this was not confirmed by the other three studies.

The use of HFOV as a rescue therapy for preterm babies not responding to conventional management has not been evaluated by a randomised controlled trial and there is no convincing evidence of its benefit in more mature babies. The use of HFOV as the primary mode of ventilatory support in preterm babies with respiratory failure has been shown to have no effect on mortality and it has not been convincingly shown to reduce the incidence of clinically significant BPD.

Inhaled nitric oxide (NO)

Nitric oxide is an endogenous vasodilator which is produced by vascular endothelium and induces relaxation of underlying smooth muscle cells. Inhaled NO is rapidly inactivated by binding to haemoglobin and therefore has vasodilator effects specific to the pulmonary circulation (unlike other pulmonary vasodilators). Pulmonary hypertension is a common feature in infants with respiratory failure. Inhaled NO may improve oxygenation in these infants through either a reversal of extrapulmonary shunting or a redistribution of pulmonary blood flow and enhanced ventilation-perfusion matching.

It has recently been shown that NO can reduce the need for ECMO in term neonates with severe respiratory failure.[8] In a randomised controlled trial in preterm neonates at high risk for developing BPD, NO has been shown to cause a short term reduction in the oxygenation index and the pulmonary artery pressure.[9] However, our own (unpublished) observations in this population have shown that these effects were not sustained and did not reduce mortality or the incidence of BPD. Further multicentre clinical trials of the use of NO in sick neonates are in progress.

Liquid ventilation

There are three theoretical advantages to ventilating the lung with liquid rather than gas. Firstly, removal of the air/fluid interface within the alveolus results in a reduction of surface tension and an associated increase in compliance;[10] secondly, lung volume may be recruited by inflation of atelectatic alveoli;[11] and thirdly, the continuous alveolar lavage provided by liquid ventilation may be of benefit by reducing the alveolar load of inflammatory mediators.

Several groups have explored liquid ventilation in animal models using different liquids.[12] Although saline was the first liquid to be studied, the poor solubility of respiratory gases in saline made it unsatisfactory for use. Successful liquid ventilation has been achieved using oxygenated oils. None of the oils used were suitable for long term ventilation because of their direct toxic effects on the lungs.

The perfluorocarbons (PFCs) are biologically inert, clear, colourless liquids which have a higher density than the tissues and are immiscible with body fluids. They are able to dissolve large amounts of respiratory gases. These physical properties make them a potentially

Theoretical advantages of liquid ventilation with perfluorocarbons
- Reduction of surface tension with improvement in pulmonary compliance
- Recruitment of atelectatic alveoli
- Continuous alveolar lavage
- High respiratory gas solubility
- Biologically inert

suitable medium for use in liquid ventilation (see box). Perflubron – the PFC used in the paper by Leach *et al*[13] – is an eight carbon chain in which all of the available binding sites are occupied by fluoride apart from one terminal position which is occupied by bromide, making the compound radio-opaque.

The first reported experience with liquid ventilation using perfluorocarbons was by Clark and Gollan in 1966[14] who described the method in spontaneously breathing mice. Two methods of mechanical ventilation with PFCs have subsequently been developed. Total liquid ventilation (TLV) requires filling of the lungs with PFC and the generation of a tidal volume of PFC using a specifically designed liquid ventilator. The physical properties of PFCs – notably, the higher density and viscosity and the slower gas diffusion rates – mean that effective gas exchange can only be performed in TLV using slow rate ventilation.[10] In partial liquid ventilation (PLV), or perfluorocarbon associated gas exchange (PAGE), the lung is filled with PFC to a functional residual capacity and a tidal volume of gas is generated using conventional gas ventilation. Both techniques have been shown to improve gas exchange in animal models of lung injury and respiratory failure.[15 16] A recent study[17] has suggested that lung compliance is greater during TLV than PLV, although this may have been due to the method used to assess compliance.

Liquid ventilation has been used in various animal models of acute lung injury and ARDS.[15–19] It has also been used in neonatal animals with hyaline membrane disease,[20–22] congenital diaphragmatic hernia,[23 24] and meconium aspiration syndrome.[25] These studies have shown that the technique can be used to achieve successful ventilation in these situations.

Liquid ventilation decreases the severity of experimental lung injury.[17] It is likely that this is due to a reduction in barotrauma or in the intra-alveolar concentration of inflammatory mediators by continuous alveolar lavage. However, it has been suggested that PFCs may have a direct effect on the inflammatory process.[26] Clearly, if PFCs are shown to exert a direct anti-inflammatory effect, they cannot be considered as biologically inert and studies of the long term biological effects will be necessary.

Liquid ventilation in humans was first described in 1990 by Greenspan *et al*[27] who reported its use in three moribund neonates. Each of the subjects had two short cycles of TLV (3–5 minutes) separated by 15 minutes of conventional gas ventilation. Two of the three babies had an increase in Pao_2 after liquid ventilation and all showed an increase in lung compliance. In a later report by the same group[12] a further three babies were studied and similar findings were reported. All six babies subsequently died as predicted prior to their recruitment.

The group in Ann Arbor, Michigan have published a series of papers documenting their experience of the use of PLV in humans. This work describes PLV with daily dosing of perflubron for up to seven days in neonatal, paediatric, and adult patients, all of whom were also concurrently receiving ECMO for their severe respiratory failure.[28–32] They reported an increase in pulmonary compliance in all groups over a three to four day period of treatment and an increase in indices of oxygenation in all groups over the same time. Short term improvements in these parameters were also found in the group of babies with congenital diaphragmatic hernia shortly after each dose of perflubron. All of these patients were also receiving numerous other therapeutic interventions. The lack of control data from these studies makes it impossible to determine to what extent PLV was responsible for any of the observed improvements in the physiological parameters. Five of the 10 adults, all six of the children, and two of the four neonates survived their illness. The lack of control data also makes it impossible to determine whether PLV contributed to an improvement in survival. The patients in these studies had numerous other clinical problems, but these were felt to be in keeping with their underlying severe illness rather than a consequence of the PLV. Again, lack of control data make it impossible to assess properly the role of PLV in the development of these problems. Small pleural leaks of perflubron occurred in a few patients who had developed pneumothorax, but these appeared to cause no major clinical problems and resolved spontaneously.

The paper by Leach *et al*[13] is a description of the use of PLV in a group of 13 neonates with severe respiratory failure. Eight of the 10 babies treated using the study protocol survived. These babies were too small to have undergone ECMO. There are no other reports of liquid ventilation in humans in peer reviewed journals, although some data are beginning to appear in abstract form[33] and clinical trials are currently underway in North America.

Practical aspects of use

In the study by Leach *et al* infants received PLV with perflubron and conventional time cycled, pressure limited ventilation. The mean amount of perflubron instilled was 15 ml/kg over a mean period of 25 minutes. Additional perflubron was given to replace evaporative losses to maintain a meniscus in the endotracheal tube. While perflubron was being instilled, ventilator settings were altered to maintain reasonably constant tidal volume. If liquid ventilation became more widespread, the rate of instillation and replacement of perflubron together with the amount used may have to be more critically evaluated.

An attempt was made to return to gas ventilation after 48 hours of beginning perflubron instillation based on the premise that it takes approximately this length of time for the lung to mature in response to other interventions such as antenatal corticosteroids and surfactant. This may only apply in the immediate newborn period. In the study infants were treated any time up to five days of age. At this stage an acute inflammatory response in the lung is likely to have occurred and the response of the lung to any intervention is likely to be different from the response in the immediate newborn period. Thus, the optimal length of time to use perflubron may be different (longer or even shorter).

The decision to resume liquid ventilation for a maximal cumulative treatment of 96 hours was made if the oxygenation index increased to a value that was 30% higher than the value when PLV was stopped. The threshold for resuming liquid ventilation is likely to have

Table 1 Predictive value of various parameters of arterial oxygenation in term infants

Parameter	Risk criteria threshold	Predicted mortality
A–aDo$_2$		
Loe[37]	>600 mm Hg for 12 hours	90%
Short[38]	>610 mm Hg for 8 hours	80%
Krummel[39]	>600 mm Hg for 12 hours	94%
Beck[40]	>610 mm Hg for 8 hours	79%
Kirkpatrick[41]	>620 mm Hg for 6 hours	100%
a/A ratio		
Ortega[42]	<0.04	83%
Oxygenation index (OI)		
Bartlett[43]	>40	80%
Ortega[42]	>60	79%

A–aDo$_2$ = alveolar–arterial oxygen tension difference; a/A = ratio of arterial to alveolar oxygen tension.

been an empirical one. In order to calculate sample size appropriately and accurately, the evaluation of the need to resume liquid ventilation in any randomised trial of its efficacy might be better studied as a separate issue once the outcome is determined for a short course of liquid ventilation.

Is it safe?
The prime aim of the study by Leach *et al* was to assess the safety of PLV. This was assessed on the basis of heart rate, blood pressure, chest radiographs, cranial ultrasonographic studies, and clinical laboratory values obtained during liquid ventilation. The authors admit that the ability to identify complications of PLV was limited by the uncontrolled design of their study and the small number of infants. A number of complications ascribed to prematurity occurred – specifically, intracranial haemorrhage, pneumothorax, and upper gastrointestinal haemorrhage. That liquid ventilation did not contribute to any of these and, indeed, was not a contributing cause in those infants who died cannot be completely ruled out. It was suggested that endotracheal tube obstruction and transient hypoxaemic episodes might have been related to the PLV. The material obtained from the blocked endotracheal tubes was mucoid in nature and viscous and tenacious. It appeared in greater amounts than during gas ventilation and could be removed by suctioning with saline. The authors speculated that this material may have been a preexisting exudate, endogenous surfactant, previously ad-

ministered exogenous surfactant, or even a newly formed airway exudate. Clearly, the incidence and effect of this acute complication will need to be monitored if liquid ventilation is increasingly used.

Animal and adult studies indicate that acute toxic effects are unlikely with the blood concentrations found in the patients in this paper. The rate of evaporation of perflubron was not as rapid as was expected and some remained evident on the chest radiograph as long as 28 days later. The long term effect of this is unknown.

Might it have a beneficial effect in the short term?
The paper describes a number of short term outcome measures in infants who have received liquid ventilation including changes in arterial oxygen and carbon dioxide tensions (Pao$_2$ and Paco$_2$), dynamic compliance, ventilatory requirements, and oxygenation index.

One concern of the authors of this paper is that three infants who had refractory hypercapnia and received high frequency ventilation were withdrawn from PLV because of recurrent hypercapnia. These infants do not appear to have been included in the analysis of short term outcome measures although it is arguable that these three infants were the most severely ill of the group. Despite this, two of them survived, which casts some doubt on the severity of risk of infants entered into the study.

Fractional inspired oxygen concentration, Paco$_2$, mean airway pressure, and oxygenation index all decreased in association with PLV and dynamic compliance of the lung increased. On the face of it, therefore, PLV is associated with an improvement in short term outcome in selected infants. However, the baseline range of many of the parameters of short term outcome that were measured was wide. Improvements associated with PLV should be accepted with caution until similar outcomes in a control group have been compared.

Might it have a benefit in the long term?
The main question with any new experimental treatment must be whether the incidence of significant long term outcome measures is altered by the use of such a treatment. Death, chronic lung disease, and neurodevelopmental outcome are arguably the main long term outcome measures which are important in neonatal medicine.

Some early clinical trials of other therapies in newborn infants with severe respiratory failure have selected infants with a poor prognosis for "rescue" treatment.[34–36]

Table 2 Surfactant failure in preterm infants

Study	Surfactant	Definition	Incidence*	Mortality#
Fujiwara[52]	Surfactant TA	Increase in a/A by <0.2 and decrease in MAP by <2 cm H$_2$O until 129 hours after surfactant	22%	35%
Charon[51]	Surfactant TA	a/A <0.3 at 24 hours of age	45%	38%
Collaborative European Multicentre Study Group[50]	Curosurf	a/A <0.3 at 24 hours after surfactant	60%	30%
Segerer[49]	Curosurf	Decrease in Fio$_2$ by <50% within 6 hours of surfactant	51%	44%
Hamvas[53]	Exosurf	Decrease in OI by <25% within 6 hours of surfactant	50%	22%
Kuint[48]	Curosurf	Increase in a/A by <0.112 one hour after surfactant	50%	45%

a/A = ratio of arterial to alveolar oxygen tension; MAP = maximum arterial pressure; Fio$_2$ = fractional inspired oxygen.
* Incidence of incomplete response to surfactant; # Mortality associated with surfactant failure.

LEARNING POINTS

∗ Partial liquid ventilation with perfluorocarbons can be used to provide ventilatory support in preterm infants.

∗ It is associated with short term improvements in pulmonary compliance and gas exchange.

∗ The use of historical controls in the assessment of new therapeutic strategies may be misleading because of a constantly changing clinical environment.

∗ The use of partial liquid ventilation in the treatment of neonatal respiratory failure must be evaluated in the context of a randomised controlled trial in a high risk population.

Prognosis was assessed using data from retrospective studies. Parameters of oxygenation and/or respiratory support were used to identify a "high risk" group in whom the mortality was expected to exceed 80–90%.[37–43] Although various such attempts to quantify disease severity in term and preterm infants have been made (tables 1 and 2), there is still little consensus regarding the criteria which are the most reliable predictors of eventual outcome. Few methods of assessing disease severity have been validated prospectively.[44 45] Nevertheless, clinical studies using such criteria to predict mortality have often reported improved survival in treated infants and, generally, the authors have concluded that their results provide evidence that a particular intervention is effective. This has led to criticism of the use of historical controls in this way.[46 47]

In uncontrolled studies one of the difficulties in assessing the effectiveness of any intervention is the uncertainty in predicting the likely outcome if the infants had been managed conventionally. Advances in "conventional" neonatal management have resulted in a constantly changing environment in which the efficacy of any new treatment needs to be evaluated. Any assessment of disease severity developed in one population at a given time cannot therefore necessarily be reliably applied to a different population at a different time.

The paper by Leach *et al* suggests that the infants treated with PLV were at "high risk of morbidity or death on the basis of the lack of a sustained response to surfactant therapy". A number of studies have demonstrated an association between an infant's initial response to surfactant and eventual outcome.[48–53] The reported incidence of "surfactant failure" in these studies of preterm infants varies from 22% to 60% (table 2). The variation probably reflects inconsistencies in definition, surfactants used, and ventilatory management, but differences in infant populations are also likely to have been important. The value of any prognostic index therefore needs to be questioned until its usefulness has been validated prospectively, preferably in a separate population.

In the study of Leach *et al* an assessment of risk based on the authors' own population would have been preferable in order to be more certain that they were dealing with a high risk group. The proportion of survivors in infants receiving liquid ventilation was 54–62%, depending on whether one includes infants withdrawn from the study and whether one classifies the infant who died of severe lung disease at five months as a "survivor". This survival rate is similar to that in our own unit for a group of infants with similar baseline oxygenation indices who were treated with conventional ventilation; our observations have shown that the predicted mortality in a preterm infant with an oxygenation index of >30 is approximately 65%. This again high-

lights how vital it is to calculate risk with conventional treatment in one's own population, at least when comparing the results of a pilot study of an experimental treatment using historical controls.

The data presented in the paper by Leach *et al* do not suggest that PLV leads to improved survival in severe respiratory distress syndrome although, as previously discussed, the technique appears feasible and possibly safe in the short term. There are unanswered questions as to its long term safety and only a larger randomised trial can yield information on its long term efficacy.

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